# Physicochemical and Biological Data for the Development of Predictive Organophosphorus Pesticide QSARs and PBPK/PD Models for Human Risk Assessment


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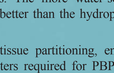
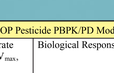
## Introduction

During the last ten years there has been a great deal of interest among scientists in building and inter-relating QSAR and PBPK/PD models for predicting risk from human exposures to toxic chemicals based on animal toxicological studies (Wilson et al., 1995). This interest recently resulted in the development of an organophosphorus pesticide exposure and risk PBPK/PD model within the Exposure Related Dose Estimating Modeling (ERDEM) platform (Blancato et al., 2000). The successful use of the model encouraged us to explore the literature for additional laboratory animal and human PBPK data to apply to assessments of aggregate exposure and cumulative risk. Central to the interpretive value of PBPK/PD models is the development and use of predictive QSAR (quantitative structure/activity relationships) models to obtain the parameters needed in PBPK models (Wilson et al., 1995). This review provides information on QSAR modeling, reports the findings of a literature search for physicochemical and biological data on new organophosphorus pesticides, and evaluates the quality of the published biological data for building predictive QSAR and PBPK/PD models.

## OPs of Interest

Thirty-one OP pesticides of interest (Table 1) were selected on the basis of the presence of aromatic or heterocyclic rings and not according to regulatory relevance. The OP pesticides are limited to three classes based on the alkylphosphorus moiety and leaving group (Kagagi et al., 1995).

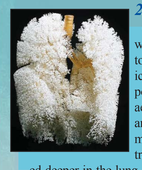
### Table 1

| Class 1 Aryl | | | | |  | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Common Name | R1 | R2 | X1 | X2 | b | c | d | e | f |
| bromophos | OMethyl | O-Methyl | S | O | Cl | H | Br | Cl | H |
| chlorthion | OMethyl | O-Methyl | S | O | H | Cl | NO2 | H | H |
| cyanophos | OMethyl | O-Methyl | S | O | H | H | CN | H | H |
| dicapthon | OMethyl | O-Methyl | S | O | Cl | H | NO2 | H | H |
| fenchlorphos | OMethyl | O-Methyl | S | O | Cl | H | Cl | Cl | H |
| fenitrothion | OMethyl | O-Methyl | S | O | H | H | NO2 | CH3 | H |
| fenthion | OMethyl | O-Methyl | S | O | H | H | SCH3 | CH3 | H |
| iodofenphos | OMethyl | O-Methyl | S | O | Cl | H | I | Cl | H |
| parathion-methyl | OMethyl | O-Methyl | S | O | H | H | NO2 | H | H |
| bromophos-ethyl | OEthyl | O-Ethyl | S | O | Cl | H | Br | Cl | H |
| chlorthiophos | OEthyl | O-Ethyl | S | O | Cl | H | SCH3 | H | Cl |
| dichlofenthion | OEthyl | O-Ethyl | S | O | Cl | H | Cl | H | H |
| fensulfothion | OEthyl | O-Ethyl | S | O | H | H | SHOCH3 | H | H |
| parathion-ethyl | OEthyl | O-Ethyl | S | O | H | H | NO2 | H | H |
| fenamphos | NHisoPropyl | O-Ethyl | O | O | H | H | SCH3 | H | H |
| isofenphos | NHisoPropyl | O-Ethyl | S | O | CO-OCH(CH3)2 | | H | H | H |
| prothiofos | Sn-Propyl | O-Ethyl | S | O | Cl | H | Cl | H | H |
| sulprofos | Sn-Propyl | O-Ethyl | S | O | H | H | SCH3 | H | H |
| trichloronat | Ethyl | O-Ethyl | S | O | Cl | H | Cl | Cl | H |
| **Class 2 Complex** | | | | |  | | | | |
| phenthoate | OMethyl | O-Methyl | S | SCH-OCOEt | H | H | H | H | H |
| phenkapton | OEthyl | O-Ethyl | S | SCH2S | Cl | H | H | Cl | H |
| phoxim | OEthyl | O-Ethyl | S | ON=C-CN | H | H | H | H | H |
| tetrachlorvinphos | OMethyl | O-Methyl | O | OC=CCl | Cl | H | Cl | Cl | H |
| chlorfenvinfos | OEthyl | O-Ethyl | O | OC=CCl | H | H | Cl | H | Cl |
| carbophenothion | OEthyl | O-Ethyl | S | SCH2S | H | H | Cl | H | H |
| fonofos | Ethyl | O-Ethyl | S | S | H | H | H | H | H |
| temephos | OMethyl | O-Methyl | S | O | H | H | S-Aryl | H | H |
| **Class 3 Heterocyclic** | | | | |  | | | | |
| etrimfos | OMethyl | O-Methyl | S | O | H | OC2H5 | =N= | C2H5 | =N= |
| chlorpyrifos | OEthyl | O-Ethyl | S | O | Cl | H | Cl | Cl | =N= |
| diazinon | OEthyl | O-Ethyl | S | O | H | CH3 | =N= | iPropyl | =N= |
| thionazin | OEthyl | O-Ethyl | S | O | H | =N= | H | H | =N= |

### A. Absorption



***1. Gastrointestinal Tract.*** First order rate constants for the absorption ($h^{-1}$) of pesticides from the gastrointestinal tract are usually estimated from gavage data using a pharmacokinetic model. Timchalk et al. (2002) modeled the oral absorption (gavage) of chlorpyrifos using a two-compartment model describing absorption from the stomach (KaS, $h^{-1}$) and the intestinal tract (KaI, $h^{-1}$). Dietary uptake was modeled by Timchalk et al. (2002) as a zero-order process based on the equations used to describe uptake from drinking water (Andersen et al., 1987 and Corley et al., 1994).



***2. Respiratory Tract.*** Considerable blood/air partition data was found in the literature pertaining to the uptake of volatile organic chemicals. Several models have been proposed for the uptake of chemicals in aerosols (water droplets). The models are complex dealing with the impingement of the droplets in the respiratory tract with small droplets being deposited deeper in the lung. The models have not been generally applied to pesticides. The low volatility of OP pesticides was considered to be the primary limiting factor for obtaining relevant partition coefficient data.

***3. Skin.*** Partition coefficients are used in PBPK/PD models to indicate the transfer of materials (distribution) between skin and blood. Jepson et al. (1992, 1994) developed data on the partitioning of parathion and paraoxon between skin and blood using Millipore Low Binding cellulose filters (molecular weight cutoff of 10,000) to separate parathion in solution from parathion bound to skin. Human autopsy skin was used by Menczel et al. (1983) to determine partition coefficients for malathion between epidermis-rich (2.72), dermis tissues (2.74) and inner skin (1.70) with aqueous buffer. Skin binding decreased 2-fold when dialyzed against simulated plasma. Reifenrath et al. (1991) studied the effect of varying partition coefficients (paraoxon and parathion) on percutaneous penetration and the extent of dermal retention in pigskin, in-vivo and in-vitro. Airflow over the skin surface significantly increased evaporative losses for parathion, while increasing the applied dose of parathion and paraoxon from 4 to 1000 $\mu g/cm^2$, resulted in a lower percentage in the dermis. The more water-soluble paraoxon penetrated the dermis better than the hydrophobic parathion.

The absorption, metabolic, tissue partitioning, enzyme inhibition, and recovery parameters required for PBPK/PD models are given in Table 2.

### Table 2

Table 2. Biological parameters required for OP Pesticide PBPK/PD Models.[a/]

| Absorption/Distribution: | Metabolic rate constants, $V_{max}$, $K_m$ | Biological Response |
|---|---|---|
| Gastrointestinal Tract, in $hr^{-1}$ | | |
| Respiratory Tract: Blood/air Blood/saline | P-450 reactions Hydrolases Transferases | $LD_{50}$, oral, dermal $IC_{50}$, inhibition of 'B' esterases Rate constants: inhibition, aging and spontaneous reactivation and synthesis of 'B' esterases. |
| Skin: Skin/Blood Skin/vehicle Skin/air Skin Permeability Constants, $K_p$, cm/hr $K_{p\text{-vapor/sc}}$ $K_{p\text{-liquid/sc}}$ $K_{p\text{-neat/sc}}$ $K_{p\text{-water/sc}}$ | $V_{max}$, in µmol/h/kg of Body weight $K_m$, in µM | |
| Tissues: Tissue/air Tissue/blood Tissue/saline | | |

[a/] Blancato et al. (2000)

Where C is the concentration gradient of the chemical in skin ($g/cm^3$), l is the thickness of the path length (cm), $k_m$ is the partition coefficient of the chemical in skin (unitless), D is the diffusion coefficient ($cm^2/h$), and $K_p$ is the permeability constant (cm/h) (Mattie et al. 1994). Dividing the absorbed dose by the applied dose and multiplying by 100 determine fractional or percent absorption. Despite the large number of percutaneous absorption studies conducted with OP pesticides, very little information is available on their maximum rate of penetration (Jflux, $ug/cm^2/h$) or permeability ($K_p$, cm/h). Provisional estimates of $K_p$ have been obtained by QSAR (Dary et al., 1998) as adapted from the equation of Potts and Guy (1992):

$$\textbf{Log } K_p \textbf{ (cm/hr)} = -2.72 + 0.71 \textbf{ Log } P_{(oct/w)} - 0.0061 \textbf{ MW}$$

$$\mathbf{n} = 89,\ \mathbf{r} = 0.817,\ \mathbf{r}^2 = 0.667,\ \mathbf{s} = 0.748$$

### B. Tissue Distribution

Tissue: Blood partition coefficients are needed in PBPK/PD models to mathematically describe the distribution of parent compounds and their metabolites in body fluids and tissues (Knaak et al., 1995). In most cases, parent OP compounds and metabolites are nonvolatile chemicals, lipophilic or hydrophilic in character that readily distribute between blood and body tissues before they are eliminated in urine, respiratory air, or via the gastrointestinal tract.

One method for obtaining partition coefficients involves the use of ultrafilters to separate phases (i.e., saline and tissue) after the chemical has been distributed (Jepson et al., 1994; Sultatos et al., 1990; Murphy et al., 1995). This procedure was applied to only parathion.

### C. Metabolic Pathway

Data are required to construct a PBPK model describing the fate of pesticides. OP pesticides undergo oxidative desulfuration, N-dealkylation, O-dealkylation, O-dearylation, thioether oxidation, side group oxidation, and hydrolysis. Water-soluble hydrolytic products such as the alkyl phosphates are eliminated directly, while leaving groups with limited solubility are conjugated with glucuronic or sulfuric acids prior to elimination (Nigg and Knaak, 2000). Maximum reaction velocity ($V_{max}$) and half-maximal ($K_m$ ) rate constants for the desulfuration of parathion to paraoxon, chlorpyrifos to chlorpyrifos-oxon, isofenphos to isofenphos oxon, and azinphosmethyl to azinphosmethyl oxon by rat or mouse liver P-450 isozymes are limited to the few OPs shown in Tables 3 and 4.

### Table 3

Table 3. Desulfuration (P=S to P=O) of Parathion to Paraoxon by Rat Liver P-450 isozymes.

| Enzymes 9000 g supernatant | Source[a/] Rat Liver | $V_{max}$, µmol/h/kg of bw[b/] 135.9 | $K_m$, µM 10.2 | $V_{max}/K_m$ ratio 13.3 | Reference(s) Wallace and Dargan, 1987 |
|---|---|---|---|---|---|
| P450 mix | Rat Liver | 95.2 | 0.35 | 272.0 | Ma and Chambers, 1994 |
| P450 mix | Rat Liver | 61.4[c/] | 17.9 | 3.4 | Norman et al., 1974 |
| P450 mix/age related | Rat Liver | 53.5[d/] | 23.8 | 2.20 | Atterberry et al., 1997 |
| P450 mix | Rat Liver | 301.9[c/] | 9 .0 | 33.5 | Murray and Butler, 1994 |
| | Mean | 129.6 | 12.3 | 10.5 | |

[a/] Male rats were used.
[b/] Literature values converted to µmol/h/kg of body weight (47.5 mg of microsomal protein/ g liver, 33 g liver/Kg of body weight).
[c/] Spectral content, 0.8 nmol of P-450/mg of microsomal protein.
[d/] Spectral content, 0.4 nmol of P -450/mg of microsomal protein.

### Table 4

Table 4. Desulfuration (P=S to P=O) of Chlorpyrifos, Isofenphos and Azinphosmethyl to their respective oxons by Rat/or Mouse Liver P-450 isozymes.

| Enzymes | Source[a/] | $V_{max}$, µmol/h/kg of bw[b/] | $K_m$ µM | $V_{max}/K_m$ ratio | Reference(s) |
|---|---|---|---|---|---|
| Chlorpyrifos | | | | | |
| P-450 mix | Rat Liver | 12.5 | 1.11 | 11.3 | Ma and Chambers, 1994 |
| P-450 mix | Rat Liver | 94.0 | 6.1 | 15.4 | Tang et al., 2001 |
| P-450 mix | Rat Liver | 80[c/] | 2.86[c/] | 28[c/] | Timchalk et al., 2002 |
| Isofenphos | | | | | |
| P450 mix | Rat Liver | 71.6 | 14.1 | 5.1 | Knaak et al., 1993 |
| Azinphosmethyl | | | | | |
| P450 mix | Mouse Liver | 182.2 | 37.5 | 4.9 | Sultatos and Minor, 1987 |

[a/] Male rats were used.
[b/] Literature values converted to µmol/h/kg of body weight (47.5 mg of microsomal protein/g liver, 33 g liver/Kg of body weight)
[c/] PBPK/PD model.

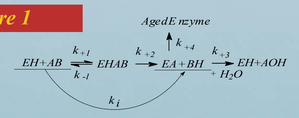
The number and/or the quality of the values given in the Tables are insufficient to generate a QSAR equation for predicting $V_{max}$, $K_m$ values for the 31 OPs of interest using the rat or mouse data. Reproducible values (i.e., $V_{max}$, $K_m$) for the P-450 catalyzed oxidative hydrolysis of the OPs and the hydrolysis of their toxic oxons by 'A-esterases' were not found in the literature for building QSAR equations for the 31 OPs.

No $V_{max}$, $K_m$ values were found for children of varying ages, however, the development of functional P-450 activity is viewed as being limited in newborns, but increasing in the first year of life to levels in toddlers and older children that generally exceed adult capacity (Cresteil, 1998).

### D. Response

Bimolecular rate constants, $k_i$ ($pM^{-1}\ h^{-1}$) are used to describe inhibition of the B-esterases (acetylcholin-, butyrylcholin- and carboxyl-) by the toxic oxons formed during their metabolism. The rate constants are derived from the reaction of OPs (AB) with 'B'-esterases (EH) to form Michaelis-Menten complexes (EHAB), phosphorylated enzymes (EA) and leaving groups (BH) as shown in Figure 1.

***Figure 1***




The bimolecular reaction, $k_i$, is the overall reaction involving the formation of the Michaelis-Menten complex (EHAB) and the phosphorylated enzyme (EA), where $K_a$, $K_d$, $K_A$, $k_{+2}$ and $k_i$ are related as follows:

***Figure 2***

$$K_a = \frac{k_{-1}}{k_1} = K_a = \frac{1}{K_A}$$

$$\frac{k_{+2}}{K_d} = K_A * k_{+2} = k_i$$

Bimolecular rate constants on the 31 OPs of interest were found in the literature for only a few of the OPs. Reactivation, synthesis, and aging of B-esterases rates are used in blood, liver and brain to account for the depletion and replacement. Rate constants for aging ($k_a$ or $k_{+4}$) and reactivation ($k_s$ or $k_{+3}$) of the phosphorylated enzyme are shown in Table 5.

### Table 5

Table 5. Rate Constants for Aging and Reactivation of ChE in human plasma.

| Pesticide groups | Aging $k_a$ ($h^{-1}$) x $10^2$ | Aging $t_{1/2}$ (h) | Reactivation $k_s$ ($h^{-1}$) x $10^2$ |
|---|---|---|---|
| Room Temperature | | | |
| di-methoxy | 2.9[a/] | 23.6 | 1.10[a/] |
| di-ethoxy | 1.8[a/] | 38.9 | NC |
| methoxy, phenyl | 1.9[a/] | 37.4 | 0.61[a/] |
| Ethoxy, ethyl | 0.26[a/] | 266.5 | NC- |
| Ethoxy, thiopropyl | 7.1[a/] | 9.8 | 0.66[a/] |
| Body Temperature | | | |
| di-methoxy | 12.5[b/] | 5.5 | 3.21[b/] |
| di-ethoxy | 5.5[b/] | 12.6 | NC |
| Ethoxy, thiopropyl | 15.45[b/] | 4.5 | 1.48[b/] |

Source: Mason, 1993.
di-methoxy (naled, 300 -76-5); di-ethoxy (triazophos, 24017 -47-8)
methoxy, phenyl (leptophos oxon, 25006 -32-0), ethoxy, ethyl (fonofos, 944 -22-9)
ethoxy, thiopropyl (prothiofoxon, 38527 -91-2)
[a/] 22°C
[b/] 37°C
NC, no convergence

## IV. Examples of Predictive OP QSAR Equations

A. *Metabolic* constants, $V_{max}$ and $K_m$ values: Table 6 gives the combined $V_{max}$, $K_m$ data of the corresponding dialkyl p-nitrophenyl phosphates from a series of dialkyl p-nitrophenyl phosphorothioates and the formation of the corresponding phenyl substituted diethylphosphates from phenyl-substituted diethylphosphorothioates by rabbit liver microsomes.

### Table 6

Table 6.

| Alkyl Substituent[a/] | $V_{max}$ (nmol/20 min/mg protein) | $K_m$ (M x $10^{-4}$) |
|---|---|---|
| Methylparathion | 11.5±0.3[c/] | 7.1±0.8[c/] |
| Ethylparathion | 12.6±0.4 | 31.0±2.3 |
| Propyl | 14.9±0.6 | 17.6±2.1 |
| Butyl | 14.9±0.6 | 13.7±1.7 |
| **Phenyl Substituent[b/]** | | |
| p-$NO_2$ (ethyl parathion) | 15.94±1.73 | 31.8±17.5 |
| m-$NO_2$ | 15.63±0.41 | 20.2±2.8 |
| m-$CF_3$ | 7.94±0.37 | 48.2±7.2 |
| p-Cl | 7.35±0.10 | 27.0±1.7 |
| Unsubsituted | 9.04±0.18 | 24.6±2.2 |
| m-$CH_3$ | 8.53±0.34 | 69.3±9.0 |
| p-$CH_3$ | 7.23±0.53 | 68.9±13.8 |
| p-$OCH_3$ | 7.78±0.40 | 31.6±6.3 |

$V_{max} = -0.05142 * Volume + 18.63 * xp10 + 0.279 * SdO + 15.9665$
$R^2 = 0.981$, n = 11, F = 118.4 Cross validation RSS = 13.44
$K_m = -56.63 * ABSQ + 24.19 SsCH_3 + 2.222 * SsF + 40.3213$
$R^2 = 0.9522$, n = 11, F = 46.48

Source: [a/]Wolcott, Va ughn and Neal (1972) and [b/]Wolcott and Neal (1972).
[c/] Value s are the means ±SD.

QSARIS™ (SCIVISION, Academic Press) was used to obtain the $V_{max}$ and $K_m$ equations involving three descriptors [(Volume, xp10 and SdO) and (ABSQ, SsCH3 and SsF)]. The $V_{max}$, $K_m$ training sets were well described by the regression equations and are statistically significant. Cross-validation showed that the constructed $V_{max}$ model (P=S to P=O) might be used to predict the value of $V_{max}$ outside the 'training set.' However, cross-validation was not possible with the $K_m$ model, and therefore predicting values of $K_m$ may be problematic. Table 7 gives the predicted rabbit liver $V_{max}$ values (P=S to P=O) for OPs of interest with the value for parathion at the top and chlorpyrifos at the bottom. The value for Isofenphos appeared somewhat in the middle of Table 7.

### Table 7

Table 7. Predicted Rabbit $V_{max}$ values (nmol/20 min/mg of protein and umol/hr/kg of bw) using QSAR equation in Table 6 and values for Structural descriptors in QSARIS™.

| name | Volume | SdO | xp10 | nmol/20 min /mg of protein | umol/hr /kg of bw |
|---|---|---|---|---|---|
| **ethylparathion** | 211.733 | 21.0083 | 0.195008 | 14.575 | **433** |
| tenephos | 294.352 | 0 | 0.716016 | 14.1729 | 421 |
| dicapthion | 183.635 | 21.0102 | 0.034021 | 13.0205 | 387 |
| **methylparathion** | 178.362 | 20.8231 | 0 | 12.6055 | **374** |
| fenitrothion | 191.229 | 21.2647 | 0 | 12.0671 | 358 |
| chlorthion | 197.262 | 21.0958 | 0 | 11.7098 | 348 |
| fensulfothion | 235.271 | 11.2542 | 0.195008 | 10.6429 | 316 |
| **isofenphos** | 288.228 | 12.1567 | 0.270991 | 9.58757 | **285** |
| phenthioate | 224.379 | 12.0706 | 0.092946 | 9.52866 | 283 |
| carbophenothion | 227.871 | 0 | 0.203647 | 8.54719 | 254 |
| thionazin | 188.007 | 0 | 0.072169 | 7.64393 | 227 |
| fonofos | 184.06 | 0 | 0.030084 | 7.17452 | 213 |
| diazinon | 231.618 | 0 | 0.141059 | 6.68511 | 199 |
| phenkapton | 271.372 | 0 | 0.249608 | 6.66367 | 198 |
| cyanophos | 184.064 | 0 | 0 | 6.50191 | 193 |
| sulprofos | 253.965 | 0 | 0.180351 | 6.26822 | 186 |
| phoxim | 250.936 | 0 | 0.171722 | 6.26316 | 186 |
| prothiofos | 240.098 | 0 | 0.129726 | 6.03791 | 179 |
| etrimfos | 229.16 | 0 | 0.099436 | 6.03048 | 179 |
| trichloronat | 214.197 | 0 | 0.057241 | 6.01909 | 179 |
| fenchlorphos | 204.906 | 0 | 0.027778 | 5.94782 | 177 |
| chlorthiophos | 252.149 | 0 | 0.154745 | 5.88442 | 175 |
| dichlorfenthion | 228.139 | 0 | 0.072169 | 5.58036 | 166 |
| methylbromophos | 214.213 | 0 | 0.027778 | 5.46925 | 162 |
| fenthion | 204.61 | 0 | 0 | 5.44544 | 162 |
| iodofenphos | 223.435 | 0 | 0.027778 | 4.995 | 148 |
| ethylbromophos | 246.255 | 0 | 0.086703 | 4.91965 | 146 |
| **chlorpyrifos** | 252.293 | 0 | 0.086703 | 4.60917 | **137** |

### Table 8

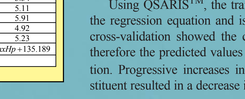
Table 8. Structures of Phosphoramidates and Bimolecular Rate Constants for the inhibition of Bovine erythrocyte AChE.

| Compound | | | | | $k_i$, $M^{-1}\ min^{-1}$ | Log $k_i$, $M^{-1}\ min^{-1}$ |
|---|---|---|---|---|---|---|
| No. | R1 | R2 | X | Y | BACHE | BACHE |
| 1 | H | H | H | O | $1.7 \times 10^8$ | 8.23 |
| 2 | H | H | Me | O | $4.5 \times 10^8$ | 6.65 |
| 3 | H | Et | H | O | $9.6 \times 10^8$ | 5.98 |
| 4 | H | n-Pr | H | O | $5.0 \times 10^9$ | 5.70 |
| 5 | H | i-Pr | H | O | $1.6 \times 10^9$ | 5.20 |
| 6 | H | t-Bu | H | O | $2.0 \times 10^{10}$ | 4.30 |
| 7 | Me | Me | H | O | $1.2 \times 10^{4}$ | 4.08 |
| 8 | H | Me | Cl | O | $1.2 \times 10^{9}$ | 6.08 |
| 9 | H | Et | Cl | O | $3.5 \times 10^{5}$ | 5.54 |
| 10 | H | n-Pr | Cl | O | $1.3 \times 10^{6}$ | 5.11 |
| 11 | H | Et | $NO_2$ | O | $8.2 \times 10^{5}$ | 5.91 |
| 12 | H | Et | MeO | O | $8.4 \times 10^{4}$ | 4.92 |
| 13 | H | Et | Me | O | $1.7 \times 10^{5}$ | 5.23 |

$Log k_i = -0.6854 * LogP + 1.542 * xp5 - 15.01 * SiN + 22.71 * MaxHp + 135.189$
$r^2 = 0.992$, n = 13, F = 249.3 Cross validation RSS = 37.04

Source: Zerba and Fukuto, 1978

B. *Inhibition* rate constant, ki : Zerba and Fukuto (1978) examined the effects of a series of ethyl a-cyanobenzaldoxime N,N-dialkyl phosphoramidates on bovine erythrocyte acetylcholinesterase (BAChE). The basic structure of these phosphoramidates is given below, with their substituent groups ($R_1$, $R_2$, Y and X) and $k_i$ ($M^{-1}\ min^{-1}$) values in Table 8.




Using QSARIS™, the training set is very well described by the regression equation and is statistically significant. However, cross-validation showed the constructed model is unstable and therefore the predicted values of log $k_i$ should be used with caution. Progressive increases in the size of the amido alkyl substituent resulted in a decrease in anticholinesterase activity.

## Conclusions and Recommendations

1. The predictive value of QSAR equations for supporting the development of OP PBPK/PD models is highly dependent on quality data.
2. Our QSAR and PBPK/PD modeling tests indicate that the quality of the existing data needs to be improved through the development of standardized protocols.
3. This review supports studies to obtain:
   - Skin permeation constants ($K_p$, cm/h) for pesticides coming in contact with skin.
   - Water/skin partition coefficient data for pesticides in water that come in contact with skin.
   - Tissue/blood partition coefficients for parent pesticides and their metabolites.
   - Metabolic parameters (i.e., $V_{max}$ and $K_m$) for parent pesticides and their metabolites.

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